# Enantioselective Synthesis of (−)-Pumiliotoxin C from a Chiral Amino Ester and an Acetylenic Sulfone that Acts as an Alkene Dipole Equivalent

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A new synthesis of the naturally occurring (−)-enantiomer of the dendrobatid alkaloid pumiliotoxin C (**1**) was achieved by the conjugate addition of methyl (−)-*cis*-2-amino-*trans*-6-methylcyclohexanecarboxylate (**3**) to 1-(*p*-toluenesulfonyl)-1-pentyne (**4**), followed by intramolecular acylation to afford (4a*S*,5*R*,8a*R*)-4a,5,6,7,8,8a-hexahydro-5-methyl-2-propyl-3-(*p*-toluenesulfonyl)-4-quinolinone (**2**). The acetylenic sulfone thus acts as the synthetic equivalent of an alkene dipole species. The required enantiopure amino ester **3** was obtained by an approach based on pig liver esterase (PLE)-mediated hydrolysis. Thus, the (−)- and (+)-enantiomers of racemic dimethyl *trans*-3-methylcyclohexane-*cis*,*cis*-1,2-dicarboxylate (**6**) afforded the corresponding half-esters **7** and **8**, respectively, when treated with PLE. The desired half-ester **7** was recovered intact after selective conversion of the free carboxylic acid group of the byproduct **8** into its benzyl ester. Half-ester **7** was converted into enantiopure (−)-**6** with diazomethane, followed by regioselective saponification and Curtius rearrangement to afford the required enantiopure key intermediate **3**. Finally, hydrogenation of the enol triflate of enaminone **2**, followed by reductive desulfonylation, afforded the product (−)-**1**.

The dendrobatid alkaloids are components of the toxic skin secretions of certain neotropical frogs of the genera *Phyllobates* and *Dendrobates*, as well as of several other species of toads and frogs.[1,2] These secretions act as a chemical defense against predation and have also been used as blowgun dart poisons by hunters of indigenous tribes, such as the Emberá Chocó of Colombia.

Pumiliotoxin C (**1**) is a relatively abundant member of the decahydroquinoline class of dendrobatid alkaloids. Major sources are the species *Dendrobates pumilio*[2g] and *Dendrobates auratus*.[2e,f] Nevertheless, it was reported that 2540 frogs were required to afford 80 mg of the alkaloid.[2g] The isolation and structure determination of **1** was reported in 1969 by Daly et al.,[3] and the absolute configuration of the naturally occurring (−)-enantiomer was established to be (2*S*,4a*S*,5*R*,8a*R*).[2h] Pumiliotoxin C is one of the less toxic dendrobatid alkaloids and acts as a reversible blocker of the nicotinic acetylcholine receptor channel.[4] It is therefore of interest in pharmacological studies of nerve and muscle systems. The poor availability of **1** in nature, from relatively exotic sources, and its interesting and potentially useful biological activity have prompted a number of approaches to its synthesis. These include syntheses of racemic **1**,[5] the natural enantiomer (−)-**1**,[6] and the unnatural antipode (+)-**1**.[7]

(1) For reviews, see: (a) Witkop, B.; Gössinger, E. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Science: New York, 1983; Vol. 21, Chapter 5. (b) Daly, J. W.; Spande, T. F. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1986; Vol. 4, pp 1−274.

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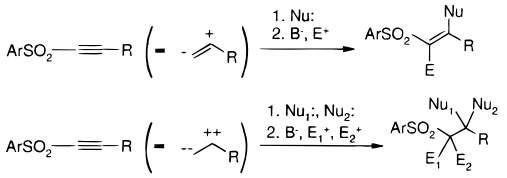
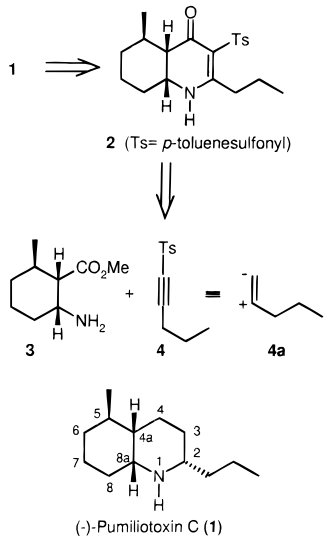
**Scheme 1**



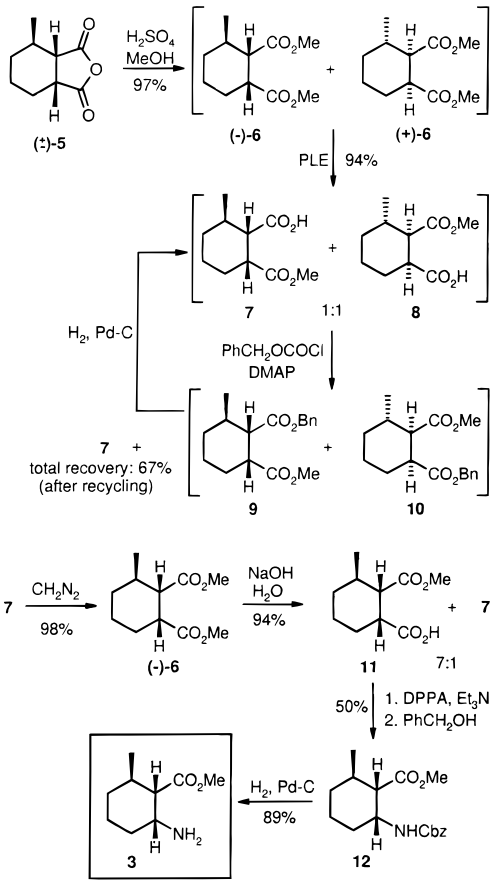
**Scheme 2**



We now report a relatively concise enantioselective synthesis of (−)-**1** based on the use of an acetylenic sulfone as the synthetic equivalent of an alkene dipole in a key cycloaddition sequence.[8] Unsaturated sulfones are valuable compounds in organic synthesis.[9] The electron-withdrawing sulfone group activates an adjacent alkene or alkyne toward conjugate addition and renders vinyl and acetylenic sulfones useful dienophiles in cycloadditions. Moreover, the products of conjugate or cycloadditions are saturated or vinyl sulfones that often contain relatively acidic α-protons, providing a site for incorporating electrophiles via the corresponding anions. Finally, the sulfone moiety can be employed as a disposable activating group in such processes, since it can be reductively removed at the end of a synthetic protocol. In this manner, acetylenic sulfones act as the synthetic equivalents of dipole or "multipole" species,[10] as in Scheme 1.

Our approach to (−)-pumiliotoxin C is outlined retrosynthetically in Scheme 2. The two key intermediates **3** and **4** afford enaminone **2** by conjugate addition of the amino group of **3** to the acetylenic sulfone moiety of **4**,[11] followed by intramolecular acylation of the resulting enamine sulfone by the ester group.[12] The sulfone **4** thus acts as the synthetic equivalent of the hypothetical alkene dipole **4a**. Preferential hydrogenation of the enaminone from the exo side then regulates the stereocenter at C-2 and reductive removal of functional groups

**Scheme 3**



completes the synthesis of **1**. We also report a new stereoselective synthesis of the (−)-enantiomer of **3**, which was required in enantiopure form for the enantioselective synthesis of (−)-**1**.

## Results and Discussion

The preparation of the required (−)-**3** was recently reported in six steps from a chiral intermediate that was itself derived from (*R*)-(+)-pulegone.[13] The *p*-toluenesulfonamide of the antipode (+)-**3** had been prepared earlier by a relatively lengthy sequence and was eventually employed in the synthesis of (+)-**1**.[7c] Our approach to (−)-**3** is shown in Scheme 3. The known racemic anhydride **5** is readily available from the Diels−Alder reaction of piperylene with maleic anhydride,[14] followed by hydrogenation and equilibration in the presence of a tertiary amine.[15] The corresponding racemic diester **6** was then subjected to hydrolysis with pig liver esterase

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(9) For reviews, see: (a) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993. (b) Fuchs, P. L.; Braish, T. F. *Chem. Rev.* **1986**, *86*, 903. (c) Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107. (d) Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951. (e) Tanaka, K.; Kaji, A. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; Wiley: Chichester, 1988; Chapter 15.

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(13) Davies, S. G.; Bhalay, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1595.

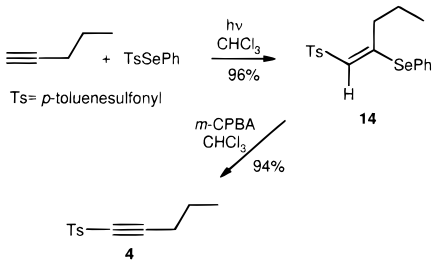
(14) Frank, R. L.; Emmick, R. D.; Johnson, R. S. *J. Am. Chem. Soc.* **1947**, *69*, 2313.

(15) Craig, D. *J. Am. Chem. Soc.* **1950**, *72*, 1678.

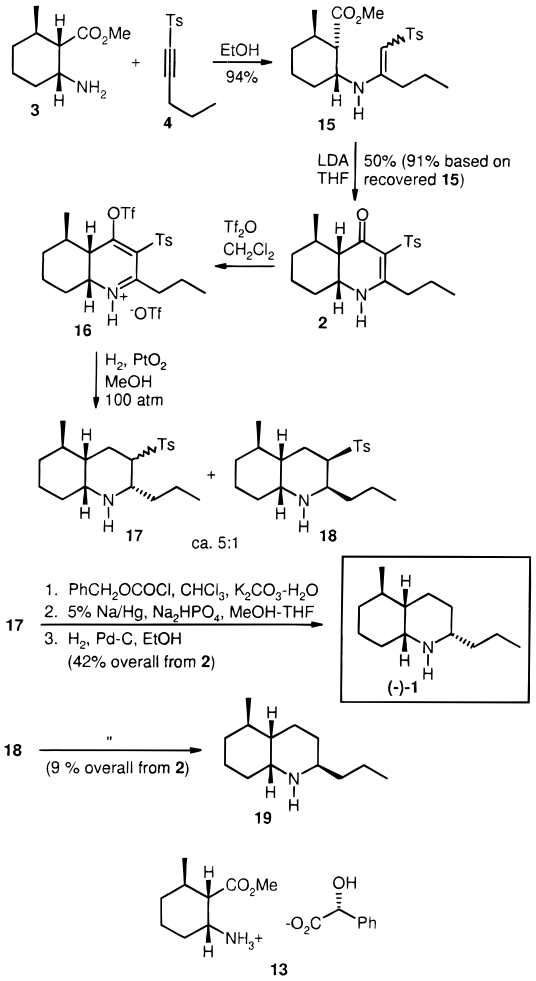
(PLE),[16] in the hope of achieving a kinetic resolution. However, when the hydrolysis was stopped at 50% completion, substantial amounts of both enantiomers had been consumed, affording the corresponding half-esters **7** and **8** in the ratio of 3:1, which was too inefficient for the purpose at hand. The hydrolysis was therefore permitted to go to completion, whereupon the enantiomers (−)-**6** and (+)-**6** underwent hydrolysis to afford the half-esters **7** and **8**, respectively, as the principal products.[17] The mixture of **7** and **8** proved difficult to separate and was therefore treated with benzyl chloroformate and DMAP,[18] resulting in the selective conversion of the undesired half-ester **8** into the mixed diester **10**, and only partial conversion of **7** into the corrresponding diester **9**. Thus, the unreacted isomer **7** was recovered in 56% yield (based on the amount of **7** in the initial mixture of **7** and **8**), while an additional 11% was obtained by recycling the mixture of diesters **9** and **10** through hydrogenolysis and reesterification.[19] The recovered **7** was then converted into the required enantiopure dimethyl ester (−)-**6**[20] with diazomethane, followed by regioselective saponification to afford a 7:1 mixture of half-esters **11** and **7**. The unseparated products were subjected to a Curtius rearrangement with diphenylphosphoryl azide (DPPA)[21] and trapped with benzyl alcohol, at which stage the desired product **12** was easily separated from the analogous regioisomer derived from **7**. Hydrogenolysis of the Cbz group then provided the required key intermediate (−)-**3** in >95% purity, as determined by NMR integration of the spectrum of the corresponding salt **13**, formed with (*R*)-mandelic acid. Enantio- and diastereomerically pure (within the limits of NMR detection) **3** was easily recovered by recrystallization of **13**, followed by basification.[22,23] This procedure therefore provides a concise approach to the enantiopure diester (−)-**6** and amino ester (−)-**3**

The remainder of the synthesis of (−)-**1** proceeded as planned. The required acetylenic sulfone **4** was obtained by selenosulfonation of 1-pentyne, followed by selenoxide elimination of the adduct **14** (Scheme 4).[24] The conjugate addition of (−)-**3** to **4** afforded adduct **15**, which cyclized to the key intermediate enaminone **2** in high yield upon treatment with LDA (Scheme 5). Hydrogenation of the corresponding enol triflate **16** occurred stereoselectively from the exo side and provided decahydroquinoline stereoisomers **17** (mixture of C-3 epimers) and **18** (pure C-3 epimer) in the ratio of 5:1. Reductive desulfonylation[25] of the Cbz derivative of **17**, followed by deprotection, then afforded (−)-pumiliotoxin C (**1**) in 42% overall yield from enaminone **2**, while the similar treatment of **18** provided 2-epipumiliotoxin C (**19**) in 9% yield from **2**.

**Scheme 4**




**Scheme 5**




(16) (a) Toone, E. J.; Werth, M. J.; Jones, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 4946 and references therein. (b) Ohno, M.; Otsuka, M. *Org. React.* **1989**, *37*, 1. (c) Zhu, L.-M.; Tedford, M. C. *Tetrahedron* **1990**, *46*, 6587.

(17) By analogy to the PLE-mediated hydrolysis of dimethyl *cis*-1,2-cyclohexanedicarboxylate, and from the active site model described by Jones et al. for the latter compound (ref 16a), we had hoped to obtain **11** directly from (−)-**6**. Unfortunately, the different behavior of the methyl-substituted cyclohexane diester necessitated the more circuitous approach shown in Scheme 3. A similar switch in the stereoselectivity of hydrolysis of dimethyl *cis*-1,2-cyclopropanedicarboxylate by PLE was reported when methyl groups were introduced at the 3-position. See: Schneider, M.; Engel, N.; Hönicke, P.; Heinemann, G.; Götisch, H. *Angew. Chem., Int. Ed Engl.* **1984**, *23*, 67.

(18) Kim, S.; Lee, J. I.; Kim, Y. C. *J. Org. Chem.* **1985**, *50*, 560.

(19) Efforts to separate the mixture of **9** and **10** by chromatography failed. Similarly, conversion of the free carboxylic acid groups of **7** and **8** to their respective esters with methyl mandelate produced inseparable mixtures.

(20) GC analysis of (−)-**6** obtained in this manner on a chiral column indicated no detectable amount of the (+)-enantiomer under conditions giving a clean separation of the enantiomers of racemic **6** (see the Supporting Information).

(21) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

(22) Since the precursor (−)-**6** was enantiopure, a very small degree of epimerization apparently occurred during the saponification or Curtius rearrangement steps leading to (−)-**3**. Enantiopure (−)-**3** obtained from recrystallized **13** was again treated with (*R*)-mandelic acid and subjected to NMR analysis to confirm that further epimerization had not taken place during the basification step.

(23) Resolution of racemic **3** via recrystallization of diastereomeric salts produced with mandelic acid proved unsuccessful. For examples of resolutions of other amines with mandelic acid and related compounds, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; p 334.

(24) (a) Back, T. G.; Collins, S.; Kerr, R. G. *J. Org. Chem.* **1983**, *48*, 3077. (b) Back, T. G.; Collins, S.; Gokhale, U.; Law, K.-W. *J. Org. Chem.* **1983**, *48*, 4776. (c) Miura, T.; Kobayashi, M. *J. Chem. Soc., Chem. Commun.* **1982**, 438.

(25) For examples of reductive desulfonylations with Na/Hg, see: ref 9c and references therein.

This approach therefore provides a relatively concise synthesis of the natural (−)-enantiomer of pumiliotoxin C from readily available starting materials.

## Experimental Section

All NMR spectra, including those shown in the Supporting Information, were obtained in deuteriochloroform. The pH 8.0 phosphate buffer was prepared according to a literature procedure.[26] Pig liver esterase (PLE) was obtained from the Sigma Chemical Company as a crude lyophilized powder from porcine liver, containing less than 5% buffer salt, 19 units/mg of solid. *m*-CPBA was purified by washing with a pH 7.5 phosphate buffer and was assumed to be 100% pure.[27] Benzyl chloroformate contained 7% benzyl chloride, as determined by NMR spectroscopy, and was used without further purification. The anhydride **5**[15] was converted to the known[28] racemic dimethyl ester **6** by the general procedure of Bussert et al.[29] GC analyses of **6** were performed on a 30 m Cyclodex-B column from J & W Scientific. *Se*-Phenyl *p*-tolueneselenosulfonate was prepared from *p*-toluenesulfonhydrazide and benzeneseleninic acid.[30] All other reagents were obtained from commercial sources and were purified as required by standard procedures.

**PLE-Catalyzed Hydrolysis of Dimethyl (±)-*trans*-3-Methylcyclohexane-*cis*,*cis*-1,2-dicarboxylate (6).** A mixture of **6** (9.449 g, 44.15 mmol) and PLE (233 mg, 100 units/mmol of **6**) in 200 mL of pH 8.0 phosphate buffer was stirred at room temperature for 5 days. During the hydrolysis, 0.5 M NaOH solution was periodically added to maintain the pH of the solution at 7−8 (total 73 mL, 36.5 mmol of NaOH). The aqueous layer was basified to pH 9.0 by the addition of more 0.5 M NaOH solution and washed with 3 × 100 mL of ether. The aqueous layer was then acidified to pH < 2 with 10% HCl solution, and the products were extracted with 3 × 100 mL of ether, dried over $MgSO_4$, and concentrated in vacuo to give 8.310 g (94%) of an inseparable mixture of **7** and **8** in the ratio of ca. 1:1 (NMR integration) as a brown oil. This was used directly in the next step without further purification.

**(−)-*trans*-3-Methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic Acid, 1-Monomethyl Ester (7).** Benzyl chloroformate (6.80 mL, ca. 44.9 mmol) and triethylamine (6.60 mL, 47.4 mmol) were added to a solution of the mixture of **7** and **8** obtained in the preceding procedure (7.905 g, 39.53 mmol) in 250 mL of dichloromethane, and the resulting mixture was stirred at 0 °C for 5 min. DMAP (5.792 g, 47.78 mmol) was added, and the mixture was stirred at 0 °C for another 30 min. It was extracted with 3 × 100 mL of 1.0 M NaOH solution, then with 10% HCl solution, brine, and dried over $MgSO_4$. The combined aqueous layers were acidified with concentrated HCl and extracted with 3 × 100 mL of ether, dried over $MgSO_4$ and evaporated under reduced pressure to afford 2.194 g (56% based on the amount of **7** in the starting material) of recovered **7** as an oil: IR (film) 3500−2500, 1738, 1726, 1699 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 11.51 (br m, 1 H), 3.64 (s, 3 H), 2.89 (m, 1 H), 2.55 (dd, $J$ = 6.8, 4.4 Hz, 1 H), 2.48−2.21 (m, 1 H), 2.08−1.83 (m, 1 H), 1.83−1.30 (m, 4 H), 1.29−1.13 (m, 1 H), 1.08 (d, $J$ = 6.8 Hz, 3 H); $^{13}C$ NMR (100 MHz) $\delta$ 179.7, 174.1, 51.3, 49.2, 40.1, 31.0, 29.4, 26.0, 20.2, 19.6; MS, *m*/*z* (rel intensity, %) 200 (7, $M^+$), 182 (58), 169 (62), 154 (73), 122 (71), 113 (71), 95 (92), 83 (100), 68 (79), 55 (90); exact mass calcd for $C_{10}H_{16}O_4$ 200.1049, found 200.1056; $[\alpha]_D^{22}$ −41.3 (*c* 1.04, $CHCl_3$).

The dichloromethane layer was concentrated in vacuo, and the crude mixture of **9** and **10** was obtained as an oil, which was hydrogenated over 10% palladium on charcoal (170 mg) in 100 mL of ethanol at room temperature and 1 atm pressure for 13 h to regenerate 5.209 g (66% recovery) of a mixture of **7** and **8** in the ratio of ca. 1:2.7. The mixture was resubjected to the above esterification procedure with benzyl chloroformate to provide an additional 426 mg (11%) of **7** (total recovery 67%).

**Dimethyl (−)-*trans*-3-Methylcyclohexane-*cis*,*cis*-1,2-dicarboxylate (6).** Excess ethereal diazomethane was added to a solution of **7** (2.580 g, 12.90 mmol) in 50 mL of methanol to give 2.715 g (98%) of (−)-**6** as a colorless oil after evaporation of the solvent: IR (film) 1739 $cm^{-1}$ (lit.[28] for racemic **6**, 1740 $cm^{-1}$); $^1H$ NMR (200 MHz) $\delta$ 3.67 (s, 3 H), 3.66 (s, 3 H), 2.88 (dt, $J$ = 6.9, 4.4 Hz, 1 H), 2.53 (dd, $J$ = 7.2, 4.6 Hz, 1 H), 2.40−2.20 (m, 1 H), 2.05−1.85 (m, 1 H), 1.80−1.45 (m, 4 H), 1.25−1.08 (m, 1 H), 1.03 (d, $J$ = 6.8 Hz, 3 H); $^{13}C$ NMR (50 MHz) $\delta$ 173.8, 173.4, 51.0, 49.3, 40.1, 31.1, 29.1, 25.9, 20.1, 19.5; MS, *m*/*z* (rel intensity, %) 214 (0.9, $M^+$), 182 (10), 154 (26), 95 (49), 40 (100); exact mass calcd for $C_{11}H_{18}O_4$ 214.1205, found 214.1213; $[\alpha]_D^{23}$ −43.8 (*c* 1.04, $CHCl_3$).

***trans*-3-Methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic Acid, 2-Monomethyl Ester (11).** A mixture of (−)-**6** (2.677 g, 12.51 mmol) and NaOH (591 mg, 14.8 mmol) in 35 mL of water was refluxed for 2.5 h and acidified with 10% HCl solution. The solution was extracted with 3 × 50 mL of ether, dried over $MgSO_4$, and concentrated in vacuo to afford 2.356 g (94%) of an inseparable mixture of **11** and **7** in a ratio of 7:1 (NMR integration) as an oil: IR (film) 3500−2600, 1736, 1705 $cm^{-1}$; $^1H$ NMR (200 MHz) (signals from **7** (vide supra) were superimposed upon the following signals assigned to **11**) $\delta$ 11.51 (br m, 1 H), 3.68 (s, 3 H), 2.88 (m, 1 H), 2.58 (dd, $J$ = 6.4, 4.6 Hz, 1 H), 2.48−2.21 (m, 1 H), 2.08−1.83 (m, 1 H), 1.83−1.30 (m, 4 H), 1.29−1.13 (m, 1 H), 1.06 (d, $J$ = 6.9 Hz, 3 H); $^{13}C$ NMR (100 MHz) $\delta$ 180.5, 173.9, 51.5, 48.9, 40.0, 30.7, 29.4, 25.7, 20.2, 19.6; MS, *m*/*z* (rel intensity, %) 200 (0.72, $M^+$), 182 (10), 168 (15), 154 (25), 122 (37), 96 (68), 95 (100), 81 (94), 67 (52), 55 (50), 41 (56); exact mass calcd for $C_{10}H_{16}O_4-H_2O$ 182.0943, found 182.0954.

**Methyl (−)-*cis*-2-[*N*-(Carbobenzyloxy)amino]-*trans*-6-methylcyclohexanecarboxylate (12).** A solution of the 7:1 mixture of **11** and **7** (2.356 g, 11.78 mmol), triethylamine (1.70 mL, 12.2 mmol), and diphenylphosphoryl azide (2.55 mL, 11.9 mmol) in 50 mL of toluene was refluxed for 4.5 h, washed with $K_2CO_3$ solution, dried over $MgSO_4$, and concentrated in vacuo to provide 2.476 g of the corresponding mixture of isocyanates as a yellow oil with IR (film): 2273, 1738 $cm^{-1}$. This was refluxed with benzyl alcohol (2.00 mL, 19.4 mmol) in 3.0 mL of pyridine for 20 min. The pyridine and excess benzyl alcohol were removed under vacuum. The residue was chromatographed over silica gel (elution with 5% ethyl acetate−hexanes) to afford 1.563 g (50% based on the amount of **11** in the mixture of starting materials) of **12** as a pale yellow oil: IR (film) 3364, 3345, 1729 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 7.37−7.30 (br s, 5 H), 5.30 (m, 1 H), 5.08 (s, 2 H), 4.16 (m, 1 H), 3.63 (s, 3 H), 2.30 (dd, $J$ = 10.1, 3.6 Hz, 1 H), 2.08−1.83 (m, 2 H), 1.83−1.50 (m, 4 H), 1.15−1.00 (m, 1 H), 0.94 (d, $J$ = 6.5 Hz, 3 H); $^{13}C$ NMR (100 MHz) $\delta$ 173.3, 155.4, 136.4, 128.0, 127.6, 66.1, 52.1, 51.1, 47.5, 32.0, 29.8, 28.6, 19.9, 19.5; MS, *m*/*z* (rel intensity, %) 305 (4, $M^+$), 170 (20), 108 (17), 91 (100); exact mass calcd for $C_{17}H_{23}NO_4$ 305.1627, found 305.1623; $[\alpha]_D^{23}$ −26.9 (*c* 1.02, $CHCl_3$).

**Methyl (−)-*cis*-2-Amino-*trans*-6-methylcyclohexanecarboxylate (3).** A solution of **12** (1.393 g, 4.567 mmol) and formic acid (0.1 mL) in 20 mL of methanol was hydrogenated for 19 h over 10% palladium on charcoal (143 mg) at room temperature and at 1 atm. The catalyst was removed by filtration through Celite, and the solvent was evaporated. The residue was triturated with 50 mL of ether and washed with 3 × 25 mL of 1.0 N NaOH solution. The ether layer was separated, dried over $MgSO_4$, and evaporated carefully without heating to afford 695 mg (89%) of **3** as a colorless oil: IR (film) 3439, 3386, 3312, 1729 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 3.69 (s, 3 H), 3.32 (m, 1 H), 2.17 (dd, $J$ = 11.1, 3.1 Hz, 1 H), 2.05−1.80 (m, 1 H), 1.80−1.40 (m, 5 H), 1.37 (br s, 2 H), 1.07−0.91 (m, 1 H), 0.88 (d, $J$ = 6.3 Hz, 3 H); $^{13}C$ NMR (50 MHz) $\delta$ 174.1, 54.4, 50.4, 47.4, 33.2, 32.3, 26.8, 19.9, 18.5; MS, *m*/*z* (rel intensity,

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%) 171 (4, $M^+$), 97 (20), 70 (23), 56 (100); exact mass calcd for $C_9H_{17}NO_2$ 171.1259, found: 171.1257; $[\alpha]_D^{23}$ −21.7 (*c* 1.06, $CHCl_3$).

The above product (662 mg, 3.87 mmol) was treated with (*R*)-mandelic acid (590 mg, 3.88 mmol) to form diastereomeric ammonium salts in the ratio of 97:3 (NMR integration). Recrystallization from 20 mL of ethanol−ether (1:3) afforded **13**: mp 104−105 °C; $^1$H NMR (200 MHz) $\delta$ 7.48−7.40 (m, 2 H), 7.33−7.20 (m, 3 H), 6.30−5.65 (br m, 4 H), 4.88 (s, 1 H), 3.70 (s, 3 H), 3.20 (m, 1 H), 2.25 (dd, $J$ = 8.8, 3.5 Hz, 1 H), 2.08 (m, 1 H), 1.80−1.30 (m, 5 H), 1.05 (m, 1 H), 0.87 (d, $J$ = 6.5 Hz, 3 H); $^{13}$C NMR (100 MHz) $\delta$ 178.3, 174.1, 142.0, 127.8, 126.9, 126.5, 74.4, 52.0, 49.7, 47.0, 31.3, 28.8, 28.0, 19.2, 18.6. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.16; H, 7.74; N, 4.33. Found: C, 63.26; H, 8.14; N, 4.36. Basification of the above salt with 1.0 N NaOH solution afforded homogeneous (NMR) **3**: $[\alpha]_D^{23}$ −24.2 (*c* 1.06, $CHCl_3$); lit.[13] $[\alpha]_D^{22}$ −31.0 (*c* 1.07, $CHCl_3$). The corresponding *p*-toluenesulfonamide was obtained from **3** and *p*-toluenesulfonyl chloride: $[\alpha]_D^{23}$ −43.3 (*c* 1.19, $CHCl_3$); lit.[13] $[\alpha]_D^{22}$ −34.3 (*c* 1.20, $CHCl_3$); lit.[7c] for the *p*-toluenesulfonamide of the antipode of **3**: $[\alpha]_D^{22}$ +34.9 (*c* 1.17, $CHCl_3$).

**(*E*)-2-(Phenylseleno)-1-(*p*-toluenesulfonyl)-1-pentene (14).** A solution of *Se*-phenyl *p*-tolueneselenosulfonate (3.02 g, 9.68 mmol) and 1-pentyne (1.60 mL, 16.3 mmol) in 8.0 mL of chloroform was placed in a 10 mm diameter glass test tube inside a water-cooled condenser, and the mixture was irradiated in a Rayonet UV reactor with 254 nm lamps for 4 h. The chloroform was evaporated and chromatography over silica gel (elution with 10% ethyl acetate−hexanes) afforded 3.52 g (96%) of **14** as a single regio- and stereoisomer (NMR) in the form of a pale green oil that crystallized from hexanes: mp 50−52 °C; IR (KBr) 1564, 1304, 1272, 1139, 1079 cm$^{-1}$; $^1$H NMR (200 MHz) $\delta$ 7.68 (d, $J$ = 8.3 Hz, 2 H), 7.55−7.26 (complex, 7 H), 5.86 (s, 1 H), 2.84 (br t, $J$ = 7.8 Hz, 2 H), 2.42 (s, 3 H), 1.64 (sextet, $J$ = 7.5 Hz, 2 H), 0.96 (t, $J$ = 7.3 Hz, 3 H); $^{13}$C NMR (50 MHz) $\delta$ 160.9, 143.7, 139.5, 136.6, 129.9, 129.7, 129.6, 126.8, 125.9, 123.9, 34.8, 23.3, 21.4, 13.6; MS, *m*/*z* (rel intensity, %) 380 (14, $M^+$), 248 (10), 223 (19), 183 (16), 157 (69), 155 (39), 139 (33), 91 (100). Anal. Calcd for $C_{18}H_{20}O_2SSe$: C, 56.99; H, 5.30. Found: C, 56.99; H, 5.34.

**1-(*p*-Toluenesulfonyl)-1-pentyne (4).**[31] A solution of *m*-CPBA (3.204 g, 18.57 mmol) and **14** (3.49 g, 9.18 mmol) in 100 mL of chloroform was refluxed for 7 h, washed with saturated $K_2CO_3$ solution, and dried over $MgSO_4$. The chloroform was evaporated, and chromatography over silica gel (elution with 10% ethyl acetate−hexanes) afforded 1.917 g (94%) of **4** as a light red oil: IR (film) 2199, 1327, 1156 cm$^{-1}$; $^1$H NMR (200 MHz) $\delta$ 7.88 (d, $J$ = 8.3 Hz, 2 H), 7.36 (d, $J$ = 8.6 Hz, 2 H), 2.46 (s, 3 H), 2.33 (t, $J$ = 7.0 Hz, 2 H), 1.58 (sextet, $J$ = 7.3 Hz, 2 H), 0.96 (t, $J$ = 7.3 Hz, 3 H); $^{13}$C NMR (50 MHz) $\delta$ 144.8, 138.9, 129.5, 126.6, 96.8, 78.2, 21.2, 20.3, 20.2, 12.9; MS, *m*/*z* (rel intensity, %) 222 (90, $M^+$), 139 (100), 129 (49), 107 (64), 91 (62), 65 (50).

**(*E*)- and (*Z*)-Methyl *cis*-2-{*N*-[2-(1-*p*-Toluenesulfonyl)-1-pentenyl]}amino-*trans*-6-methylcyclohexanecarboxylate (15).** A solution of **3** (484 mg, 2.83 mmol) and **4** (611 mg, 2.75 mmol) in 10 mL of ethanol was stirred for 20 h at room temperature. The ethanol was evaporated, and chromatography over activated neutral alumina (80−200 mesh) with 10% ethyl acetate−hexanes afforded 1.014 g (94%) of **15** as a mixture of (*E*)- and (*Z*)- isomers in the ratio of 1:2.5 (NMR integration; respective geometries determined by NOE experiments), in the form of a light yellow oil that crystallized from ether to give a white powder with the same *E*:*Z* ratio: mp 92−101 °C; IR (KBr) 3321, 1735, 1599, 1274, 1127, 1078 cm$^{-1}$; $^1$H NMR (400 MHz) (signals assigned to the (*Z*)-isomer) $\delta$ 7.81 (d, $J$ = 8.2 Hz, 2 H), 4.54 (s, 1 H), 3.60 (s, 3 H), 0.98 (d, $J$ = 6.3 Hz, 3 H); (signals assigned to the (*E*)-isomer) 7.76 (d, $J$ = 8.2 Hz, 2 H), 4.99 (s, 1 H), 3.64 (s, 3 H), 0.93 (d, $J$ = 6.5 Hz, 3 H); MS, *m*/*z* (rel intensity, %) 393 (7, $M^+$), 362 (5), 301 (7), 238 (93), 95 (69), 91 (65), 83 (100). Anal. Calcd for $C_{21}H_{31}NO_4S$: C, 64.12; H, 7.89; N, 3.56. Found: C, 63.84; H, 7.79; N, 3.44.

**4a,5,6,7,8,8a-Hexahydro-5-methyl-2-propyl-3-(*p*-toluenesulfonyl)-4-quinolinone (2).** *n*-Butyllithium (2.30 mmol) was added to a solution of diisopropylamine (320 ($\mu$L, 2.29 mmol) in 3.0 mL of THF, and the resulting solution was stirred for 15 min at −78 °C. A solution of compound **15** (758 mg, 1.93 mmol) in 5.0 mL of THF was added, and the resulting mixture was stirred for another 20 min at −78 °C and then for 40 min at room temperature. The THF was evaporated and chromatography over activated neutral alumina (80−200 mesh) with 10% ethyl acetate−hexanes, followed by ethyl acetate−methanol (2:1), afforded 339 mg (45%) of unreacted **15** as a light yellow oil and 346 mg (50%; 91% based on the amount of consumed **15**) of **2** as a pale yellow solid foam, respectively. Recrystallization from methanol gave **2** as a white powder: mp 163−164 °C; IR (KBr) 3283, 1657, 1281, 1148, 1132 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 7.88 (d, $J$ = 8.1 Hz, 2 H), 7.23 (d, $J$ = 8.0 Hz, 2 H), 5.48 (m, 1 H), 3.81 (m, 1 H), 3.19 (dt, $J$ = 13.3, 7.7 Hz, 1 H), 2.79 (dt, $J$ = 13.3, 7.7 Hz, 1 H), 2.38 (s, 3 H), 1.98−1.78 (m, 3 H), 1.73 (dd, $J$ = 10.5, 3.8 Hz, 1 H), 1.78−1.50 (m, 5 H), 1.09 (t, $J$ = 7.3 Hz, 3 H), 1.02−0.76 (m, 1 H), 0.64 (d, $J$ = 6.5 Hz, 3 H); MS, *m*/*z* (rel intensity, %) 361 (2), 360 (3), 296 (100), 269 (71), 228 (49), 190 (54), 91 (66), 41 (44). Anal. Calcd for $C_{20}H_{27}NO_3S$: C, 66.48; H, 7.48; N, 3.88. Found: C, 66.33; H, 7.44; N, 3.95. $[\alpha]_D^{23}$ +207.3 (*c* 1.01, $CHCl_3$).

**5-Methyl-2-propyl-3-(*p*-toluenesulfonyl)decahydroquinoline (17) and Its 2-Epimer (18).** A solution of **2** (115 mg, 0.319 mmol) and triflic anhydride (80 $\mu$L, 0.48 mmol) in 3.0 mL of dichloromethane was refluxed under argon for 18 h and concentrated in vacuo to afford crude **16** as a gray solid (192 mg), which was used directly in the next step. A solution of **16** (192 mg) in 6.0 mL of methanol was hydrogenated over $PtO_2$ (99 mg, 0.44 mmol) at 100 atm for 6 days. The catalyst was removed by filtration through Celite, and the filtrate was concentrated in vacuo. The residue was triturated with dichloromethane and washed with saturated $K_2CO_3$ solution. The dichloromethane layer was separated and dried over $MgSO_4$. The solvent was evaporated, and the crude material was chromatographed over silica gel (elution with 17% ethyl acetate−hexanes) to give one of the C-3 epimers of **17** containing a minor impurity.[32] Further elution with 25% ethyl acetate−hexanes gave **18** as a single diastereomer (19 mg, 17% overall from **2**). Finally, elution with ethyl acetate provided the other C-3 epimer of **17**, along with a minor impurity.[32] The first and third fractions were combined (86 mg), and this crude mixture was used directly in the next step. Compound **18** was recrystallized from hexanes to provide colorless needles: mp 113−114 °C; IR (film) 1291, 1145, 1084 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 7.75 (d, $J$ = 8.1 Hz, 2 H), 7.33 (d, $J$ = 8.1 Hz, 2 H), 3.52 (dt, $J$ = 11.4, 3.7 Hz, 1 H), 3.38 (dt, $J$ = 12.5, 4.0 Hz, 1 H), 3.03 (m, 1 H), 2.43 (s, 3 H), 2.08−1.85 (m, 3 H), 1.75−1.21 (m, 11 H), 0.96 (t, $J$ = 7.3 Hz, 3 H), 0.91−0.82 (m, 1 H), 0.47 (d, $J$ = 6.3 Hz, 3 H); $^{13}$C NMR (100 MHz) $\delta$ 144.2, 136.1, 129.6, 128.3, 60.9, 52.1, 46.3, 42.3, 35.2, 32.2, 27.4, 22.5, 21.6, 20.8, 19.2, 19.1, 13.9; MS, *m*/*z* (rel intensity, %) 349 (2.6, $M^+$), 306 (100), 194 (55), 151 (70), 91 (69), 72 (65), 41 (51); exact mass calcd for $C_{20}H_{31}NO_2S$ 349.2075, found 349.2049; $[\alpha]_D^{22}$ +20.0 (*c* 0.40, in $CHCl_3$).

(31) Compound **4** has been previously prepared by a different route: Iwata, N.; Morioka, T.; Kobayashi, T.; Asada, T.; Kinoshita, H.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1379.

(32) The impurity was tentatively identified as the 4-hydroxy derivative of **17**. No attempts were made to remove it, since it underwent reductive elimination to the $\Delta^3$ olefin with sodium amalgam and hydrogenation to the desired product **1** in subsequent steps. The indicated configuration at C-3 of **18** was established by NOE experiments conducted upon its *N*−Cbz derivative. When H-2 was irradiated ($\delta$ 4.58), 10% enhancement of the signal of H-3 ($\delta$ 3.48) was observed, while irradiation of H-3 gave 15% enhancement of the H-2 signal. Decoupling experiments of the *N*−Cbz derivative indicated $J$ = 3.6 Hz between H-2 and H-3, and $J$ = 8.3 and 11.3 Hz between H-3 and the two protons at H-4. These results are consistent with an axial hydrogen atom at C-3 and a cis relationship between H-2 and H-3. The indicated configurations at C-2 of **17** and **18** was confirmed by their respective conversions into the known products **1** and **19**, respectively.

**(−)-Pumiliotoxin C (1).** The mixture of crude epimers of **17** (86 mg) and benzyl chloroformate (370 $\mu$L, ca. 2.44 mmol) was refluxed for 3 h in 2.0 mL of chloroform and saturated $K_2CO_3$ solution (4:1), and the organic layer was separated and dried over $MgSO_4$. The solvent was evaporated and the crude material was chromatographed over silica gel with 5% ethyl acetate−hexanes to remove excess benzyl chloroformate, and then with ethyl acetate to afford the *N*−Cbz derivative of **17** (123 mg) as an oil.

The above product, $Na_2HPO_4$ (148 mg, 1.04 mmol), and 5% sodium amalgam (10.0 g, 21.7 mg-atoms of Na) in 6.0 mL of methanol−THF (1:1) was stirred at room temperature for 5 h and filtered through Celite, and the filtrate was concentrated in vacuo. The residue was triturated with dichloromethane and washed with saturated $K_2CO_3$ solution. The dichloromethane layer was separated and dried over $MgSO_4$. The solvent was evaporated and the crude material was chromatographed over silica gel (elution with 10% ethyl acetate−hexanes) to give the desulfonylated *N*-Cbz derivative of **17** (52 mg) as an oil.

A mixture of the latter product and 10% palladium on charcoal (20 mg) in 3 mL of ethanol was hydrogenated at room temperature and 1 atm for 4.5 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated in vacuo. The residue was triturated with chloroform and washed with saturated $K_2CO_3$ solution. The chloroform layer was separated and dried over $MgSO_4$. The solvent was evaporated, and the crude material was chromatographed over silica gel (elution with 5% triethylamine−hexanes) to afford (−)-pumiliotoxin C (**1**) (26 mg, 42% overall yield from **2**) as a yellow oil: IR (film) 3300 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 2.87−2.83 (m, 1 H), 2.58−2.50 (m, 1 H), 2.00−1.80 (m, 2 H), 1.75−0.88 (m, 15 H), 0.91 (t, $J$ = 6.9 Hz, 3 H), 0.85 (d, $J$ = 6.6 Hz, 3 H); $^{13}C$ NMR (100 MHz) $\delta$ 57.8, 56.0, 42.6, 39.6, 35.9, 33.3, 27.4, 27.2, 27.0, 21.2, 19.9, 19.1, 14.3; MS, *m*/*z* (rel intensity, %) 195 (4, $M^+$), 194 (8), 166 (60), 152 (100). The free base was converted to the corresponding hydrochloride salt, which was recrystallized from 2-propanol to give colorless needles: mp 289−291 °C (sealed capillary). For the (−)-enantiomer: lit.[6a] 284−288 °C; lit.[6b] 237−239 °C; lit.[6c] 286−288 °C, lit.[6d] 220−225 °C, lit.[6e] 286−288 °C; $^1H$ NMR (400 MHz) $\delta$ 9.60 (m, 1 H), 8.30 (m, 1 H), 3.33 (m, 1 H), 3.00 (m, 1 H), 2.55−2.30 (m, 2 H), 2.23−1.95 (m, 4 H), 1.92−1.84 (br d, 1 H), 1.83−1.75 (br d, 1 H), 1.72−1.35 (m, 6 H), 1.32−1.20 (m, 1 H), 1.04−0.95 (m, 1 H), 0.92 (t, $J$ = 7.4 Hz, 3 H), 0.90 (d, $J$ = 6.2 Hz, 3 H); $^{13}C$ NMR (100 MHz) $\delta$ 60.1, 58.0, 40.9, 34.8, 34.3, 29.1, 27.2, 25.2, 23.1, 20.6, 19.7, 19.1, 13.7 (these values are in excellent agreement with the literature[5b,6c]); $[\alpha]_D^{23}$ −16.8 (*c* 0.45, MeOH); lit.[6a] $[\alpha]_D^{26}$ −15.2 (*c* 0.46, MeOH); lit.[6b] $[\alpha]_D^{22}$ −12.9 (*c* 0.35, MeOH); lit.[6c] $[\alpha]_D^{21}$ −16.2 (*c* 1.00, MeOH); lit.[6d] $[\alpha]_D^{20}$ −13.1 (*c* 1.0, MeOH); lit.[6e] $[\alpha]_D^{20}$ −14.5 (*c* 1.00, MeOH).

**2-Epipumiliotoxin C (19).** Compound **18** (34 mg, 0.097 mmol) was similarly converted into 2-epipumiliotoxin C (**19**) (6.6 mg, 9% overall from **2**) as a yellow oil: IR (film) 3276 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 3.13 (dt, $J$ = 10.5, 4.1 Hz, 1 H), 2.84−2.75 (m, 1 H), 1.90−1.01 (m, 17 H), 1.00 (d, $J$ = 7.2 Hz, 3 H), 0.91 (t, $J$ = 7.0 Hz, 3 H); $^{13}C$ NMR (100 MHz) $\delta$ 50.0, 49.5, 42.0, 38.4, 32.5, 31.6, 29.7, 25.3, 20.5, 19.4, 19.3, 14.2 (these values are in good agreement with the literature,[5c] although some minor impurity signals were also evident); MS, *m*/*z* (rel intensity, %) 195 (1.6, $M^+$), 194 (3), 166 (5), 152 (100).

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**Supporting Information Available:** The $^1H$ and $^{13}C$ NMR spectra of compounds **7**, **11**, **12**, **3**, **13**, **18**, and **1**, as well as the GC (chiral column) of both (±)-**6** and (−)-**6** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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